Nociceptin/orphanin FQ peptide-receptor system: are we any nearer the clinic?

Nociceptin/orphanin FQ (N/OFQ) is a 17 amino acid peptide with activity at the nociceptin receptor (NOP), a G-protein coupled receptor related to but distinct from the opioid receptors. The functional role of this receptor, in common with classical opioid receptors (MOP-μ/DOP-δ/KOP-κ), is to affect the transmission of nerve signals, in particular those conveying nociceptive information. This is achieved by modulating voltage-gated Ca²⁺ channels, K channels, and adenylyl cyclase via an inhibitory G-protein (G_i). The full role of the N/OFQ-NOP system remains unclear, as it has actions implicated in both the suppression and enhancement of pain. This is seemingly dependent upon the anatomical site of the receptor in that anti-opioid effects/hyperalgesia are seen supraspinally and analgesia spinaly.

Since formal identification of N/OFQ, there have been major advances in the design and evaluation of novel NOP ligands. Indeed, high potency/high efficacy agonists and high potency antagonists are now readily available for laboratory use. In collaboration with colleagues in Italy (Drs G. Calo’ and R. Guerrini), we have shown recently that NOP antagonists delivered directly into the brain act as analgesics. In addition, there is industrial interest in this receptor system as a potential therapeutic target, and several patents are registered.

In this article, we summarize the available human data in order to address the question ‘are we any nearer the clinic?’ with this peptide-receptor system. Despite the perceived clinical importance of N/OFQ, there is a dearth of information concerning circulating levels in man in both normal and disease states, such as pain. In Table 1, we have summarized the measured concentrations of N/OFQ from all currently published studies.

Between the studies, a remarkable consistency may be seen in control (‘non-diseased’) levels, of the order 10 pg ml⁻¹ in plasma. This represents a circulating concentration of some 5 pM. Does this represent an accurate assessment of the situation at the effect site, that is, at the receptor? As detailed above, NOP is found both peripherally and in the central nervous system, with effects upon organs such as the heart and kidney. Accordingly, the data might reflect the concentration observed at the end organ, although no account for either metabolism or local release of the peptide, most probably from peripheral nerves, is made. In the CSF, however, the prevailing concentration appears to be much greater, in the order of 55 pg ml⁻¹, equivalent to 28 pM. Indeed, this latter concentration approaches the value (equilibrium dissociation constant for [³H]N/OFQ—46 pM, data from rat brain) for effective binding between N/OFQ and NOP, although the same arguments concerning metabolism and local release still hold.

It seems reasonable to suggest that in pain states, N/OFQ levels may change. Our logic is based on an assumption that N/OFQ may be involved in setting pain thresholds. In experiments, NOP antagonists given into the mouse brain produce an antinociceptive response. This would seem to imply that supraspinal N/OFQ-ergic tone is high, favouring ‘pain’. Switching this off might reset the threshold to yield an apparently antinociceptive response. Therefore, in pain states, a supraspinal increase in N/OFQ could be postulated with a possible decrease in the spinal cord (as N/OFQ delivery to this site produces antinociception). Is there any evidence for this and how would this present in the plasma?

Current data are conflicting in that some pain states show raised levels compared with controls and others show lower levels. Raised plasma levels, compared with controls, have been reported in both acute and chronic pain states. Indeed, a graded elevation of N/OFQ level was seen from control to chronic pain groups, through acute and subacute pain states. No difference as a result of sex was observed in the control group. It is important to note that in this study the pain was heterogeneous in nature.

In a study of fibromyalgia syndrome (FMS) patients, a significant decrease in plasma N/OFQ levels was seen for all patients compared with non-FMS controls, although the actual levels measured were unclear. Interestingly, when levels in pre-menopausal subjects were analysed according to phase of the menstrual cycle, there was a significant difference only between sufferers and equivalent (non-FMS) controls for those in the luteal phase. In cluster headache patients, decreased N/OFQ levels were also reported, compared with age- and sex-matched controls, with a post-episodic return to normal levels. This condition might be
A recurring problem with these studies, alluded to above, relates to plasma measurements: how relevant is the circulating level in plasma to what is happening in the brain, especially if the clinical end point is pain? To address this problem, in as far as is practicable in a patient population, a study measured N/OFQ levels in both plasma and cerebrospinal fluid (CSF) for pregnant women presenting either for elective Caesarean section or normal labour, requesting combined spinal epidural anaesthesia.10 The latter would presumably be in a greater state of pain. It is of significance to note that there were no differences observed in either plasma or, more importantly, CSF N/OFQ levels. On balance, the data from plasma/CSF measurements are too variable to reach any firm conclusions regarding pain at this time.

Table 1 N/OFQ levels in biological fluids of human origin. (M, male; F, female; RIA, radioimmunoassay; EIA, enzyme-linked immunosorbent assay; n/d, not determined, below detectable limits; PBC, primary biliary cirrhosis; HCC, hepatocellular carcinoma; FMS, fibromyalgia syndrome), NOP, nociceptin/orphanin FQ receptor. Data are mean (SD)

<table>
<thead>
<tr>
<th>Sample source</th>
<th>Patient group</th>
<th>Sample size</th>
<th>N/OFQ level (pg ml$^{-1}$)</th>
<th>Method</th>
<th>Notes</th>
<th>Study author, date of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>FMS Control</td>
<td>23 (F) 8 cyclic/15 non-17 (F) 8 cyclic/9 non-</td>
<td>2.6/2.3 4.0/2.5</td>
<td>RIA</td>
<td>Luteal phase—FMS/Control 2.4/4.7</td>
<td>Anderberg, 1998$^8$</td>
</tr>
<tr>
<td>CSF</td>
<td>Elective Caesarean Labour/epidural</td>
<td>10 (F)</td>
<td>52.49 (34.25) 63.39 (33.26)</td>
<td>RIA</td>
<td>Only study in CSF</td>
<td>Brooks, 1998$^{10}$</td>
</tr>
<tr>
<td>Plasma</td>
<td>Elective Caesarean Labour/epidural</td>
<td>7.59 (21.58)</td>
<td>13.73 (23.79)</td>
<td>RIA</td>
<td>NOP density also measured</td>
<td>Kumar, 1999$^{11}$</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>Knee surgery</td>
<td>10 (NOP, N/OFQ)</td>
<td>n/d</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial tissue</td>
<td>Wilson disease</td>
<td>11 (NOP)</td>
<td>13.98 (2.44)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Acute pain</td>
<td>30</td>
<td>16.65 (8.01)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Sub-acute pain</td>
<td>20</td>
<td>20.66 (8.98)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Chronic pain</td>
<td>20</td>
<td>24.44 (13.60)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Control</td>
<td>20 (10M, 10F)</td>
<td>10.65 (5.58)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Cluster headache Post-CH Control</td>
<td>14 (3F, 11M)</td>
<td>4.91 (1.96) 8.60 (1.47)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>HCC Baseline</td>
<td>22</td>
<td>9.38 (2.57)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Wilson disease PBC Liver cirrhosis Control HCC</td>
<td>26 21 15 29 29</td>
<td>14.0 (2.7) 12.1 (3.2) 12.8 (4.0) 9.2 (1.8) 105.9 (14.4)</td>
<td>RIA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hepatic disease such as hepatocellular carcinoma (HCC), primary biliary cirrhosis (PBC), and liver cirrhosis show elevated levels of N/OFQ in plasma, compared with age-matched healthy controls.12 13 In the case of the HCC patients, extremely high levels of N/OFQ were seen—whether a patient was with or without pain. Increased levels are also seen for Wilson’s disease, an hereditary disorder affecting copper metabolism with hepatotoxic effects.13 14 These studies may implicate a role for the liver in N/OFQ metabolism.

Whilst there are few studies detailing plasma levels, there are currently even fewer detailing the targeting of this system in man. N/OFQ is currently unlicensed for use in man and despite a clear pattern in animal behavioural studies, there is no correlation in humans between circulating levels and pain states, taking into account the caveats detailed above.

In one of the first studies in man, healthy subjects were injected with N/OFQ into either the temporal muscle of the face or the trapezius muscle of the back.17 The dosage was derived from both animal data and previous human studies conducted using other neuropeptides. Doses of from 12.5 to 200 pmol were used for temporal muscle injections and 200 pmol injected into the trapezius muscle. Relating this to circulatory N/OFQ levels of 5 pmol litre$^{-1}$ (giving a total circulating mass of 20–25 pmol), the implication is that the higher doses would occupy NOP with incipient effect. As might be anticipated, no pain was felt, indicating the actions of N/OFQ are more likely to be observed in the CNS.

Two studies on urological patients (in detrusor hyperreflexia)18 19 showed that administration of isotonic saline containing 1 $\mu$M N/OFQ increased bladder capacity and volume threshold for voiding reflex compared with controls. A decrease in maximum bladder pressure was also noted, but this did not reach statistical significance. The studies show evidence for therapeutic use of N/OFQ (based on the identification of NOP on C-fibre afferents and their presence in the bladder) and, more importantly, an absence of adverse effects. Further studies are required to determine optimal dose and duration of action.
Use of a nociceptin cream to combat capsaicin-induced pain in healthy, human volunteers was reported to have produced no adverse effects, no lasting effect upon plasma N/OFQ levels (57.1 pg ml$^{-1}$ before, 36.5 pg ml$^{-1}$ after; note that these are much higher than those reported in Table 1), and no change in pain response to capsaicin (E. Hashiba, K. Hirota, G. Calo’, et al. Effects of nociceptin/orphanin FQ cream on capsaicin cream-induced pain in human volunteers. Unpublished meeting abstract, 15/09/2003, Camerino, Italy).

It is clear that much further work is needed before any N/OFQ-containing or N/OFQ-like product is to be put into clinical practice. What is the most appropriate disease state—pain? Until this is defined then the appropriate clinical trial cannot be designed. Despite the plasma data described above we would predict (based on extensive small animal work) that pain at least represents a sensible starting point and that use of NOP antagonists might proceed to phase I studies, followed by ‘proof of concept’ in an acute pain model. However, these hypothetical studies require the development of small non-peptide molecules with good oral bioavailability for which the clinic still awaits.

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\+Declaration of interest

DGL holds a consultancy with Pfizer (Animal Health), Sandwich, Kent, UK.

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